Project Number: 733112

Project Acronym: SPIDIA4P

Project title:
SPIDIA for Personalized Medicine – Standardisation of generic Pre-analytical procedures for In-vitro DIAgnostics for Personalized Medicine

Publishable Report

Period covered by the report: from 01/07/2018 to 31/12/2019

Periodic report: *[1st] [2nd] [3rd] [4rd]*

1. Publishable summary

1.1.Description of project context and objectives

Started on January 1st, 2017, the goal of the 48-month project SPIDIA4P (**S**tandardisation of generic **P**re-analytical Procedures for **I**n vitro **DIA**gnostics **for P**ersonalised Medicine; www.spidia.eu) is to go the next steps towards healthcare systems improvements with worldwide impact by developing and implementing a comprehensive portfolio of 22 European pre-analytical CEN/Technical Specifications (CEN/TS) and ISO/International Standards (ISO/IS), addressing the important pre-analytical workflows applied to personalised medicine in medical laboratories. These CEN/TS and ISO/IS will also be applicable laboratory customers, in vitro diagnostics developers and manufacturers, biobanks, institutions and commercial organizations performing biomedical research, and regulatory authorities. The standard documents are thus applicable to all segments and the entire value chain which contribute to biomarker discovery, development and implementation into healthcare: high quality samples in biobanks as the decisive basis for all biomarker related work, biomedical research in the industry and other research institutions to develop biomarkers including generation of scientific evidence for these, in-vitro diagnostic (IVD) test development, and implementation and use of these IVD tests in healthcare systems. Furthermore, corresponding External Quality Assurance (EQA) Schemes will be developed and implemented by SPIDIA4P as well, aiming to survey the resulting diagnostic practice. SPIDIA4P will ensure training, education, and counselling as additional major foci of the project.

SPIDIA4P's highly successful predecessor SPIDIA laid the basis for developing and introducing the first 9 CEN/TS for pre-analytical workflows into European countries and initiated their progress to ISO/IS documents. Like SPIDIA, the current SPIDIA4P project is bringing together key experts of numerous stakeholder organisations with deep knowledge on pre-analytical and analytical procedures, European and international standardisation organisations´ processes (CEN and ISO), external quality assurance, quality management, ethics and regulatory demands.

SPIDIA4P is funded as a coordination and support action by the European Union's Horizon 2020 research and innovation programme and consists of 19 highly experienced partners from private industry including SMEs, public institutions and the European Standards Organisation CEN.

The SPIDIA4P consortium is closely interacting with various large European public research consortia to obtain access to research and validation studies data, serving as evidence for the new joint standards developments for achieving improvements of diagnosis, patient stratification and prognosis of disease outcome and for speeding up innovation in human biomarker discovery and development. Based on the success of SPIDIA coordination, QIAGEN has been renewed as Coordinator unanimously.

1.2. Descriptions of work performed and main results

During the first 36 project months, SPIDIA4P progressed the project work for all intended new CEN/TS and ISO/IS documents. This work is happening at the CEN/Technical Committee (CEN/TS) 140 for "In vitro diagnostic medical devices" and at the ISO/TC 212 for "Clinical laboratory testing and in vitro diagnostic test systems". All voting / ballots via the European

(CEN) or global National Standards Bodies (ISO) resulted in a strong support for all these new documents.

A huge success in late 2018 and during the course of 2019 was the finalization and publication of the first 8 ISO International Standards for molecular diagnostic preanalytical workflows:

- Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for
    - Formalin-fixed and paraffin-embedded (FFPE) tissue - Part 1: Isolated RNA (ISO 20166-1:2018)
    - Formalin-fixed and paraffin-embedded (FFPE) tissue - Part 2: Isolated Proteins (ISO 20166-2:2018)
    - Formalin-fixed and paraffin-embedded (FFPE) tissue - Part 3: Isolated DNA (ISO 20166-3:2018)
    - Frozen tissue — Part 1: Isolated RNA (ISO 20184-1:2018)
    - Frozen tissue — Part 2: Isolated Proteins (ISO 20184-2:2018)
    - Venous whole blood - Part 1: Isolated cellular RNA (ISO 20186-1:2019)
    - Venous whole blood - Part 2: Isolated genomic DNA (ISO 20186-2:2019)
    - Venous whole blood - Part 1: Isolated circulating cell free DNA from plasma (ISO 20186-3:2019)

In Europe these new documents replaced as EN ISO Standards the former CEN/TS documents, which were originally initiated by SPIDIA and had been introduced in Europe in 2015.

This success was enhanced by the publication of new CEN/TS standard documents in 2019 or by finalization for publication in early 2020:

- Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for
    - Saliva - Isolated human DNA (CEN/TS 17305:2019)
    - Frozen tissue - Part 3: Isolated DNA (CEN/TS 16826-3:2018)
    - CTCs in venous whole blood - Part 1: Isolated RNA (CEN/TS 17390-1:2020)
    - CTCs in venous whole blood - Part 2: Isolated DNA (CEN/TS 17390-2:2020)
    - CTCs in venous whole blood - Part 3: Preparation for analytical CTC staining (CEN/TS 17390-3:2020)

The Saliva DNA and the Frozen Tissue DNA documents have meanwhile become also projects at the ISO/TC 212 for progressing them further to ISO Standards under the Vienna Agreement.

All other planned new CEN/TS documents have become approved and running projects at the CEN/TC 140:

- *Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for*
    - *Exosomes and other extracellular vesicles in venous whole blood — Isolated RNA, DNA and proteins*
    - *Venous whole blood – Isolated circulating cell free RNA from plasma*
    - *Urine and other body fluids — Isolated cell free DNA*

- *Fine Needle Aspirates (FNA) — Part 1: Isolated cellular RNA*
- *Fine Needle Aspirates (FNA) — Part 2: Isolated proteins*
- *Fine Needle Aspirates (FNA) — Part 3: Isolated genomic DNA*
- *Human specimen — Isolated microbiome DNA*

Two additional SPIDIA4P initiated new ISO/IS documents are also meanwhile progressed projects at the ISO/TC 212:

- *Molecular in vitro diagnostic examinations - Specifications for pre-examination processes for*
  - *Metabolomics in urine, venous blood serum and plasma*
  - *Formalin-fixed and paraffin-embedded (FFPE) tissue -Part 4: in situ detection techniques*

SPIDIA4P has until now also develop the majority of the intended EQA Schemes, corresponding to the already published ISO and CEN documents and to the new upcoming SPIDIA4P CEN and ISO documents, aiming to survey the resulting diagnostic practice**.** During the first 36 project months, the 13 EQA Schemes were finally tested by SPIDIA4P consortium and partner consortia participants, published and implemented into the public available proficiency testing programme of the SPIDIA4P partner Integrated BioBank of Luxembourg (IBBL):

- Circulating Tumour Cells (CTC) Isolation and Detection
- Cell Free RNA (cfRNA) Extraction from Plasma
- CSF Aliquoting
- Viable PBMC Isolation
- DNA Extraction from Whole Blood
- DNA Extraction from FFPE Material
- DNA Extraction from Frozen Tissue
- Microbial DNA Extraction from Saliva
- Microbial DNA Extraction from Stool
- Circulating Cell Free DNA (ccfDNA) Extraction from Whole Blood
- RNA Extraction from Whole Blood
- RNA Extraction from FFPE Material
- Total RNA Extraction from Frozen Tissue

SPIDIA4P has run a quite huge portfolio of measures for the implementation and dissemination of standards and EQA Schemes. During the first 36 months, these included the launch of a new modern website including permanent updates and serving as the central hub for project information and dissemination (www.spidia.eu), various social media campaigns by almost all partners, three Newsletters sent to more than 16,000 recipients (https://www.spidia.eu/news-media/newsletter), development and release of a portfolio of e-education and e-learning/teaching materials, and a digital self-assessment tool for the assessment of the compliance of pre-analytical procedures with the published ISO Standards and published as well as upcoming CEN/TS. SPIDIA4P has also shown intensive presence at international conferences with more than 70 mostly invited talks and presentations, more than 30 training courses, meetings with professional societies, and finally a significant number of scientific and other publications (http://www.spidia.eu/publications/spidia4p-publications/). A publication highlight is a to

SPIDIA4P dedicated issue of the scientific journal New Biotechnology in 2019. A dissemination highlight was a SPIDIA4P event in the European Parliament in Brussels in March 2019 (https://www.spidia.eu/fileadmin/Images/Download/Brochures/SPIDIA4P_Brochure.pdf).

Furthermore SPIDIA4P become linked to two additional new HORIZON 2020 projects in 2019: EASI-Genomics (https://www.easi-genomics.eu/home) and EU-STANDS4PM (https://www.eu-stands4pm.eu/). The already established close co-work with other consortia successfully continued, such as with CANCER-ID (https://www.cancer-id.eu, until December 2019), CBmed (www.cbmed.at), and several others.

1.3 Expected final results and potential impact and use

The SPIDIA4P funding period will end by December 2020. SPIDA4P is on a very good track to have by then generated and implemented the comprehensive portfolio of 22 pre-analytical CEN/TS and ISO/IS documents as listed above, addressing the important pre-analytical workflows applied to Personalised Medicine. Corresponding EQA Schemes will have been developed and implemented as well, aiming to survey the resulting quality of samples and diagnostic practice.

Diagnostic errors cause about 10% of all patient deaths and about 17% of adverse events [Institute of Medicine (IOM) Report Sept. 2015]. Based on SPIDIA's and meanwhile also other consortia's broad evidence, it is expected that these CEN/TS and ISO/IS documents and their associated EQA Schemes wil significantly contribute to the sustainability of health care systems by reducing the number of diagnostic errors. The standards are of key importance as pre-analytical workflows contribute by about 50 – 70% to the laboratory diagnostic errors rate [e.g. Medical Laboratory Observer; May 2014]. Securing good quality clinical samples with molecular bioanalyte profiles as they were in the patient's body, is decisive for most of the applications in Personalized Medicine. The SPIDIA4P consortium has already achieved a broad international consensus on this view. Most of the analytical tests and applications will therefore benefit on pan-European and local scale but also globally.

SPIDIA4P's work has become also important in light of the new EU "in vitro diagnostic medical devices regulation (IVDR)" which was released in May 2017 with a 5 year' transition period (REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL). This new law contains in several paragraphs dedicated requirements for analytical test relevant pre-analytical workflow variables. The CEN/TS and ISO/IS documents are in line with these requirements of the regulation. It is therefore expected that the standards as well as the EQA Schemes will become quite relevant for translating these IVDR requirements into daily routine. SPIDIA4P authors have published a dedicated paper on this topic (https://www.sciencedirect.com/science/article/abs/pii/S1871678419300822?dgcid=coauthor).

Overall, the expected reduction of diagnostic errors will lead to improved patient stratification in Personalized Medicine, prognosis of disease outcome, improved clinical decisions and health outcomes for the benefits of patients.

As the CEN/TS and ISO/IS documents are also applicable to research and biobanks, it can be expected that the too high percentage of non-reproducible research studies will be reduced. This will lead to faster growth and benefits to the European diagnostics industry, also to SMEs working on new biomarkers and new services.